## REMARKS

Claims 1-14 are pending and under examination. Claims 1-2, 4, 7, and 9-14 have been amended. Claims 3 and 8 have been canceled without prejudice or disclaimer. Claims 15-25 have been newly added. Support for the amendments and new claims can be found throughout the specification and claims as originally filed. For example, support can be found in paragraphs [0008]-[0009], [0012], [0014], [0027]-[0028], [0031], [0034], [0045], [0051], [0061]-[0062], and [0064] of the specification. No new matter is added. Reconsideration of the pending claims are respectfully requested.

**Rejections under 35 U.S.C. § 112, First Paragraph**

Claims 10 to 13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

To overcome a *prima facie* case of lack of enablement, the burden falls on the Applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 48 F.2d 1395, 1406-7, 179 U.S.P.Q. 286, 194 (CCPA 1973), and M.P.E.P. § 2164.05. The evidence provided by the Applicant needs not be convulsive but merely convincing to one skilled in the art. *Id.* In addition, the Applicant is not precluded from providing a declaration after the filing date which demonstrates the claimed invention works. *Id.* Additionally, a declaration is, itself, evidence that must be considered. *Id.*

Applicants respectfully submit that claims 10 to 13 as amended are fully enabled by the present specification. Claim 10 as amended now recites "refractile cancer" therefore the claimed invention is not directed to cancer generally, but specifically to "refractile cancer." Applicants herein submit a signed declaration under 37 C.F.R. § 1.132 by Dr. Michael A. Palladoni, Jr., Ph.D., a Senior Vice President, Chief Technology Officer and Scientific Co-founder of Nereus

Pharmaceuticals, Inc. (hereinafter "the Palladino declaration"). Applicants submit that Nereus Pharmaceuticals, Inc. is the licensee of the present application. The Palladino declaration provides patent and scientific literature that confirms the compounds of structure (I) are useful in treating refractile mammalian cancer cells.

Enclosed herewith is the Palladino declaration that introduces scientific and patent literature that demonstrates claims 10-13 are enabled as of the filing date of the present application. Applicants submit that "NPI-0052" is an internal designation for Salinosporamide A. The scientific and patent literature listed in Appendix A of the Palladino declaration are summarized as follows:

1. U.S. Patent Application Publication No. 2005/0049294 shows that Salinosporamide A and several of its analogs are useful in treating resistant human uterine cells and resistant leukemia cells. Examples 34 and 42 show that Salinosporamide A, compound II-2, compound II-4, compound II-17 and compound II-18 are active against MES-SA/Dx5 (a multidrug resistant human uterine sarcoma cell line). Example 19 and Table 2 also show that Salinosporamide A is cytotoxic against OVCAR-3, a resistant ovarian cancer cell line.

2. U.S. Patent Application Publication No. 2009/0036390 shows that Salinosporamide A is useful in treating resistant multiple myeloma cells. Example 6 and Figure 5A demonstrate that Salinosporamide A is active against several resistant multiple myeloma cell lines, for example, MM.1R (Dexamethasone-resistant multiple myeloma cell line) and Dox-40 (Doxorubicin-resistant multiple myeloma cell line). Example 6 and Figure 5B also show that Salinosporamide A induces apoptosis in 4 patients suffering from multiple myeloma that were refractory to Bortezomib therapy, and 5 patients having multiple myeloma that were resistant to Thalidomaide and Dexamethasone.

3. U.S. Patent Application Publication No. 2009/0148445 discloses Salinosporamide A and its analogs are useful in treating therapy-resistant cancers, such as non-Hodgkin's lymphoma. Examples I-VII and Figures 1-19 show Salinosporamide A is useful against resistant cancer cells, for example, B-NHL Ramos cells and resistant B-NHL-Daudi cells.

4. U.S. Patent Application Publication No. 2009/0156469 discloses Salinosporamide A and its analogs are useful for treating Waldenstrom's Macroglobulinemia, including resistant Waldenstrom's Macroglobulinemia. Waldenstrom's Macroglubulinemia is a biologically unique low-grade B-cell lymphoma. Example 38 indicates that Salinosporamide A is useful in treating resistant Waldenstrom's Macroglobulinemia cells.

5. PCT Publication No. WO 2008/124699 discloses that Salinosporamide A and its analogs are useful for treating resistant cancers. Examples 38 and 40 show that Salinosporamide A is active against gemcitabine-resistant human pancreatic carcinoma cells and mPANC (a drug-resistant mesenchymal pancreatic tumor), respectively.

6. U.S. Patent Application No. 12/329,518 discloses that Salinosporamide A and its analogs are useful for treating resistant cancers. Example 35 shows that Salinosporamide A is active against resistant myeloma cells.

7. R. Andtbacka *et al.*, (unpublished manuscript) demonstrates that Salinosporamide A is useful in treating resistant human pancreatic cancer cells.

8. D. Chauhan *et al.*, Cancer Cell, 8:407-419 (2005) demonstrates that Salinosporamide A is useful in treating resistant multiple myeloma cells.

9. A. Roccaro *et al.*, Blood (March 2008) demonstrates that Salinosporamide A is useful in treating resistant Waldenstrom;s Macroglobulinemia cells. As provided previously, Waldenstrom's Macroglobulinemia is a biologically unique low-grade B-cell lymphoma.

10. J. Cusack *et al.*, AACR. (2005) shows that Salinosporamide A is useful in treating resistant pancreatic cancer cells.

11. E. Suzuki *et al.*, ASH (2005) demonstrates that Salinosporamide A is useful in treating resistant Daubi B-NHL clones. Daubi B-NHL clones are non-Hodgkin's lymphoma clones.

12. S. Khanbolooki *et al.*, AACR (2006) shows that Salinosporamide A is useful in treating resistant pancreatic carcinoma cells.

13. R. Andtbacka *et al.*, AACR (2006) shows that Salinosporamide A is useful in treating resistant pancreatic cancer cells.

14. A. Barral, *et al.*, AACR (2007) demonstrates that Salinosporamide A is useful in treating resistant prostate cancer cells.

Thus, in view of the disclosure of the present application and the references included with the Palladino declaration, Applicants submit that one skilled in the art would understand that the compounds of claim 10 are useful in treating refractile mammalian cancer cells.

Further, Applicants respectfully submit that one skilled in the art would not be subject to undue experimentation. Applicants note that "[t]he enablement requirement is met if any description enables any mode of making and using the claimed invention." *Engel Industries, Inc.* v. *Lockformer Co.*, 20 U.S.P.Q.2d 1300 (Fed. Cir. 1991). Also, limiting the Applicant to preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting progress in the useful arts. *See* M.P.E.P. § 2164.08(c). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See* M.P.E.P. § 2164.01(a). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *Id.*

The Examiner has already acknowledged that the level of one skilled in the art is "high" (see page 4 of the Office Action mailed March 9, 2011). In addition, as discussed previously, Claim 10 is amended to the treatment of "refractile" (refractory) cancers. Also, the present application discloses that salinosporamides, such as those encompassed by claim 10, are "excellent candidates" for use in the treatment of refractile cancers (see paragraph [0051] of the specification). Furthermore, the Palladino declaration demonstrates the quality of experimentation would not be unreasonable. Taken together, one skilled in the art would not be subject to undue experimentation. Applicants respectfully submit that any further experimentation is not undue, and is typically engaged by those on skill in the art when a compound is found to exhibit such therapeutic activities as Salinosporamide A. Thus, claim 10 is fully enabled. Claims 11-13 depend from claim 10 (claims 14-23 depend directly or through one or more claims from claim 10) and are therefore fully enabled. Take altogether, Applicants

submit that the claimed invention are fully enabled under the Federal Circuit case law. Accordingly, withdrawal of the lack of enablement rejection is respectfully requested.

**Rejections under 35 U.S.C. § 112, Second Paragraph**

Claims 1 to 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "sulfonyl" and claims 1, 8, and 10 do not end in a period.

Without acquiescing to the Examiner's assertions and to expedite prosecution of the claimed invention, the rejected term "sulfonyl" has been deleted in currently amended claims 1 and 10. In addition, claims 1 and 10 as amended now end in a period. Claim 8 has been canceled without prejudice or disclaimer, rendering rejection against claim 8 moot. Accordingly, withdrawal of the indefiniteness rejection is respectfully requested.

**Double Patenting Rejections**

Claims 1 to 9 are rejected on the ground of non-statutory obviousness-type double patenting over claims 1 to 15 of US 7,176,232.

Claims 1-8 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-18 of co-pending application No. 12/638,860.

Claims 10 to 14 are rejected on the ground of non-statutory obviousness-type double patenting over claims 1 to 3 of US 7,126,233 and claims 1 to 27 of US 7,635,712.

Claims 8 and 9 are rejected on the ground of non-statutory obviousness-type double patenting over claims 1 to 15 of US 7,179,834.

Applicants respectfully traverse the double patenting rejections, however based on the present claim amendments, Applicants respectfully request the Examiner to hold these rejections

in abeyance until the present application is in condition for allowance in order to reassess any alleged claim overlap.

## CONCLUSION

In view of the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge $78.00 to Deposit Account No. 07-1896 to cover the extra claims fees for three (3) additional dependent claims over twenty (20) in the present application. However, the Commissioner is authorized to charge any fees deemed necessary with the filing of this paper, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,

Date: June 9, 2011

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*Attachments*: Declaration under 37 C.F.R. § 1.132 by Dr. Michael A. Palladoni, Jr., Ph.D.
Appendix A of Declaration (list of scientific and patent literature)
Appendix B of Declaration (copies of scientific and patent literature)